

Analysis of prevalence of HIV-1 drug resistance in primary infections in the United Kingdom

Article (Published Version)

Porter, Kholoud, Pillay, Deenan, Cane, Patricia, Dean, Gill, Churchill, Duncan, Baily, Guy, Drake, Susan and Fisher, Martin (2001) Analysis of prevalence of HIV-1 drug resistance in primary infections in the United Kingdom. *BMJ*, 322. pp. 1087-1088. ISSN 1759-2151

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/37344/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Analysis of prevalence of HIV-1 drug resistance in primary infections in the United Kingdom

UK Collaborative Group on Monitoring the Transmission of HIV Drug Resistance

Abstract

Objectives To identify changes since 1994 in the prevalence of resistance to anti-HIV drugs in primary HIV-1 infections in the United Kingdom.

Design Retrospective and prospective assessment of viruses obtained from people recently infected with HIV.

Setting Multiple centres (patients enrolled in the UK register of seroconverters) and a single large HIV clinic (active case ascertainment).

Participants 69 patients infected with HIV between June 1994 and August 2000.

Main outcome measures Prevalence of key mutations associated with drug resistance in the reverse transcriptase and protease genes of HIV-1, by year of infection.

Results Between June 1994 and August 2000, 10 (14%) of 69 newly infected patients had one or more key HIV-1 mutations associated with drug resistance. The risk of being infected with drug resistant virus increased over time (adjusted relative risk per year 1.74 (95% confidence interval 0.93 to 3.27), $P=0.06$). The estimated prevalence of drug resistance in those infected in 2000 was 27% (12% to 48%).

Conclusions Transmission of drug resistant HIV-1 in the United Kingdom seems to be increasing. New approaches to encourage safer sexual behaviour in all sectors of the population are urgently needed.

Introduction

The incidence of AIDS and the mortality due to HIV-1 infection have declined dramatically in the United Kingdom since the introduction of highly active antiretroviral drugs in 1996. In contrast, the incidence of new infections has not decreased,¹ and there is evidence of increasing high risk sexual behaviour among homosexual men in London.² Since resistance to antiretroviral drugs is known to emerge in some treated patients, there is a risk that these virus variants may be transmitted, so compromising treatment in newly infected individuals.³ We decided to estimate the prevalence of transmitted (primary) resistance to anti-HIV drugs in the United Kingdom and to identify changes since highly active antiretroviral agents became available.

Participants and methods

Patients included in this study were a subset of those enrolled in the UK register of HIV seroconverters, for

whom a stored serum or plasma sample was available within 18 months of a negative result in an HIV antibody test or who were found to be infected after having had a negative result in an HIV antibody test in the preceding 18 months.⁴ Patients fulfilling these criteria who were found through active case ascertainment at a single large clinic were also included. Participants had received no antiretroviral drugs at the time of resistance testing. Nucleotide sequencing of the reverse transcriptase and protease genes of plasma virus, analysis, and subtype designations were undertaken as previously described.⁵ Drug resistance was defined as the presence of one or more key mutations in reverse transcriptase or protease recognised as being associated with reduced susceptibility to drugs.⁶

The midpoint between the dates of negative and positive antibody tests was used as the date of seroconversion. We used LOGXACT to perform logistic regression analyses on individual patients' data. We examined the association between the presence of a key mutation and the year of seroconversion, allowing for the time intervals between the dates of negative and positive antibody tests and the dates of negative and resistance tests.

Results

Of 69 patients infected between June 1994 and August 2000 (the first 20 have been reported previously³), 60 were infected with subtype B virus (the major subtype in Europe and North America) and nine by non-B (three subtype A, five subtype C, one subtype D). Fifty eight were infected through sex between men, nine (six women) through sex between men and women, and two (women) through self inflicted injury or injection. Ten (14%) had evidence of reverse transcriptase or protease gene mutations associated with drug resistance (table). In two of the 10 cases, resistance against two of the three available classes of antiretroviral agents was identified. All 10 patients were white and were infected with subtype B virus (nine through sex between men, one through self inflicted injection). As patients with a key mutation were significantly older than those in whom no key mutation was found (mean age 39.1 years *v* 31.9 years, $P=0.02$), we also included age as a factor in the logistic regression analyses. We found evidence of an increase in the risk of being infected with drug resistant virus over time (adjusted relative risk per year 1.74, 95% confidence interval 0.93 to 3.27; $P=0.06$).

Editorial by Little

Correspondence to:
D Pillay, PHLS
Antiviral
Susceptibility
Reference Unit,
Division of
Immunity and
Infection, University
of Birmingham
Medical School,
Edgbaston,
Birmingham
B15 2TT
d.pillay@bham.
ac.uk

BMJ 2001;322:1087-8

bmj.com

Full details of all
authors and their
affiliations are on
the BMJ's website

Prevalence and characteristics of primary HIV drug resistance in the UK 1994-2000

Estimated year of seroconversion	Total tested (No with drug resistance mutations)	Key mutations associated with drug resistance for each patient identified	Drugs for which mutations compromise efficacy
1994	1 (0)	—	—
1995	5 (0)	—	—
1996	15 (0)	—	—
1997	3 (1)	RT: M41L, T215L	Zidovudine
1998	10 (1)	RT: M41L, T215Y	Zidovudine
1999	9 (1)	RT: M41L	Zidovudine
2000	26 (7)	RT: K219Q	Zidovudine
		RT: T69N	Didanosine, zalcitabine
		RT: Y181C	Nevirapine, efavirenz
		RT: M41L, V108I, T215D*	Zidovudine, efavirenz, nevirapine
		RT: M41L, K103N, Y188L, T215Y	Zidovudine, efavirenz, nevirapine
		PR: L90M	Saquinavir, nelfinavir
		RT: T215D*	Zidovudine

RT=reverse transcriptase; PR=protease; C=cysteine; D=aspartic acid; I=isoleucine; K=lysine; L=leucine; M=methionine; N=asparagine; Q=glutamine; T=threonine; V=valine; Y=tyrosine.

*Although the T215D mutation does not itself confer resistance, it reflects evolution from a transmitted zidovudine resistant virus and is prone to re-emergence of resistance following initiation of therapy.⁷ It has therefore been included in the table.

Discussion

We report preliminary evidence of an increase in the transmission of drug resistant HIV-1 over time in the United Kingdom, with an estimated prevalence of 27% (95% confidence interval 12% to 48%) in people infected in 2000. It is important to study patients soon after infection to obtain the best estimates of primary drug resistance, because HIV continues to evolve after transmission and resistant virus may be less likely to be detected within the dominant plasma virus population at later time points.

At least two factors are likely to contribute to these findings. Firstly, highly active antiretroviral therapy is used more often, and the prevalence of drug resistance in people infected with HIV may be increasing. Secondly, as unprotected sex among those at highest risk of HIV infection increases, the likelihood of being infected by a person who has taken antiretroviral drugs is increased.

Nine patients with transmitted drug resistant virus in our study were infected through sex between men. However, the small numbers of other risk groups represented in our study preclude any firm conclusions being drawn about differences between risk groups in the transmission of resistant virus. Clearly, adherence to treatment in people receiving highly active

antiretroviral therapy must be improved in order to minimise the emergence of drug resistance.⁸ In addition, further work is needed to evaluate the impact of primary drug resistance on the outcome of HIV infection in such individuals. Finally, new approaches to encourage safer sexual behaviour within all sectors of the population are urgently needed.

We thank P Rice, St George's Hospital, London; F Anderson and J Mantell, St Helier Hospital, Carshalton; S Bragman, District Hospital, Greenwich; C Carne, Addenbrooke's Hospital, Cambridge; J Clarke, Clayton Hospital, Wakefield; G Downie, Crosshouse Hospital, Kilmarnock; R Duthie, Victoria Hospital, Blackpool; S El-Gadi, Homerton Hospital, London; B Goh and C Skinner, Royal London Hospital, London; R Gilson, Mortimer Market Centre, London; A Joseph, Manor Hospital, Walsall; U Joshi, Castle Hill Hospital, Cottingham; K Kumar, Queen Elizabeth Hospital, King's Lynn; J Meaden, Norfolk and Norwich Hospital, Norwich; K McLean, Charing Cross Hospital, London; P Munday, General Hospital, Watford; M Murphy, St Bartholomew's Hospital, London; P Schober and M Wiselka, Royal Infirmary, Leicester; M Shahmanesh, Whittall St Clinic, Birmingham; J Sweeney, Royal Hospital, Preston; A Tang, Royal Berkshire Hospital, Reading; and J Weber, St Mary's Hospital, London. The work of colleagues at both the PHLs Antiviral Susceptibility Reference Unit (Daina Radcliffe, Judith Workman) and MRC Clinical Trials Unit (Patrick Kelleher, Joanne Gillett, Freya Tyrer) is also acknowledged, as is invaluable statistical input from Nick Andrews.

Contributors: This paper is written by the Analysis and Writing Committee of the UK Collaborative Group on Monitoring the Transmission of HIV Drug Resistance, which comprises Kholoud Porter for the UK Register of HIV Seroconverters, Deenan Pillay and Patricia Cane for the PHLs Antiviral Susceptibility Reference Unit, Gill Dean, Duncan Churchill, Guy Bailly, Susan Drake, and Martin Fisher. Further details of the authors' affiliations are given on the *BMJ*'s website. DP is the guarantor.

Funding: This work is funded by the Public Health Laboratory Service (PHLS) and the Medical Research Council (MRC). The UK Collaborative Group on Monitoring the Transmission of HIV Drug Resistance is a collaboration between the PHLs Antiviral Susceptibility Reference Unit and the UK Register of HIV Seroconverters. The UK register is a collaboration between the MRC Clinical Trials Unit and the PHLs Communicable Disease Surveillance Centre, Department of Primary Care and Population Sciences and Department of Sexually Transmitted Diseases, Royal Free and University College Medical School.

Competing interests: Work in DP's laboratory has been supported by research and educational grants from a number of pharmaceutical companies, and DP is an occasional adviser to these companies. GD, DC, and MF have received financial support to attend conferences from various pharmaceutical companies which manufacture antiretroviral agents. DC and MF have also received funding for consultancy work for pharmaceutical companies.

What is already known on this topic

The emergence of HIV drug resistance in patients receiving antiretroviral therapy is common

Transmission of virus variants resistant to anti-HIV drugs has been documented

What this paper adds

The prevalence of transmitted HIV drug resistance in the United Kingdom is increasing, exceeding 20% in 2000

New approaches to encourage safer sexual behaviour are urgently needed

- 1 AIDS and HIV infection in the United Kingdom: monthly report. *Communicable Disease Report Weekly* 2000;10:37-40.
- 2 Dodds JP, Nardone A, Mercey DE, Johnson AM. Increase in high risk sexual behaviour among homosexual men, London 1996-8: cross sectional, questionnaire study. *BMJ* 2000;320:1510-1.
- 3 Yerly S, Kaiser L, Race E, Bru JP, Clavel F, Perrin L. Transmission of antiretroviral-drug-resistant HIV-1 variants. *Lancet* 1999;354:729-33.
- 4 UK Register of HIV Seroconverters Steering Committee. The AIDS incubation period in the UK estimated from a national register of HIV seroconverters. *AIDS* 1998;12:659-67.
- 5 Pillay D, Cane PA, Shirley J, Porter K. Detection of drug resistance associated mutations in HIV primary infection within the UK. *AIDS* 2000;14:906-8.
- 6 Hirsch MS, Brun-Vezinet F, D'Aquila RT, Hammer SM, Johnson VA, Kuritzkes DR, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAMA* 2000;283:2417-26.
- 7 De Ronde A, van Dooren M, van der Hoek L, Bouwhuis D, de Rooij E, van Gemen B, et al. Establishment of new transmissible and drug-sensitive human immunodeficiency virus type 1 wild types due to transmission of nucleoside analogue-resistant virus. *J Virol* 2001;75:595-602.
- 8 Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133:21-30.

(Accepted 17 January 2001)